

Application Number 10/540770

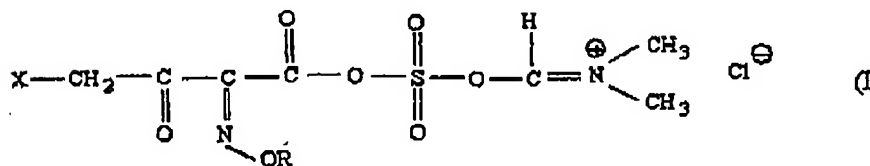
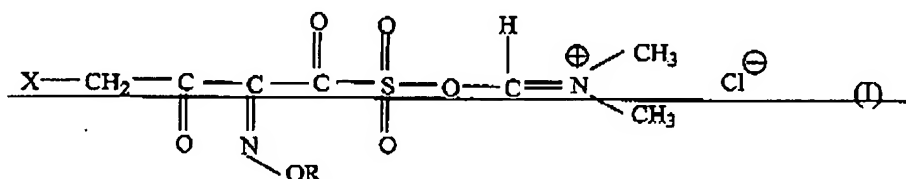
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**Amendments to the Claims:**

This listing of claims will replace all prior versions and listings of claims in the application.

**Listing of Claims:**

1. (Currently Amended) A ~~novel~~ 4-halo-2-oxyimino-3-oxo butyric acid-N, N-dimethyl formiminium chloride chlorosulfate of formula (I) useful in the preparation of cephalosporin antibiotics



wherein X is chlorine or bromine;

R is hydrogen, C<sub>1-4</sub> alkyl group, ~~an easily removable~~ a hydroxyl protective group, selected from trialkyl silyl ethers; trialkyl aryl silyl ethers; trialkyl stannyl ethers; trityl; tetrahydropyranyl; alkyl or aryl sulphonates selected from tosyl, mesyl, and besyl; boron or aluminum containing two alkyl groups; unsubstituted benzyl; or

-CH<sub>2</sub>COOR<sub>5</sub>, or -C(CH<sub>3</sub>)<sub>2</sub>COOR<sub>5</sub>;

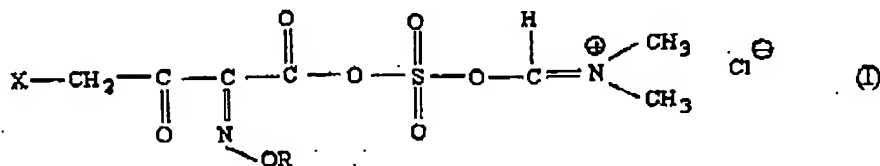
wherein R<sub>5</sub> is hydrogen; or ~~an easily a~~ hydrolysable ester group selected from lower alkyl esters; alkanoyloxy alkyl esters selected from acetoxy methyl, pivaloxy methyl,

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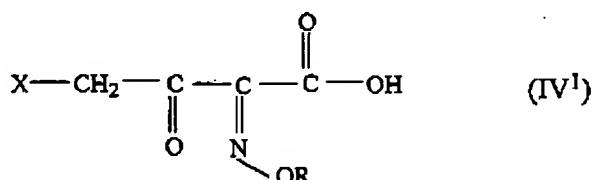
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1-acetoxy ethyl, and 1-pivaloxyethyl; lower alkoxy carbonyloxyalkyl esters; alkoxymethyl esters; lower alkyl amino methyl; benzyl ester; and cyanomethyl ester.

2. (Currently Amended) A process for preparation of compound of formula (I)



comprising reacting 4-halo-2-oxyimino-3-oxobutyric acid of formula (IV<sup>1</sup>),



wherein X is chlorine or bromine;

R is hydrogen, C<sub>1-4</sub> alkyl group, ~~an easily removable~~ a hydroxyl protective group, selected from trialkyl silyl ethers; trialkyl aryl silyl ethers; trialkyl stannyl ethers; trityl; tetrahydropyranyl; alkyl or aryl sulphonates selected from tosyl, mesyl, and besyl; boron or aluminum containing two alkyl groups; unsubstituted benzyl; or

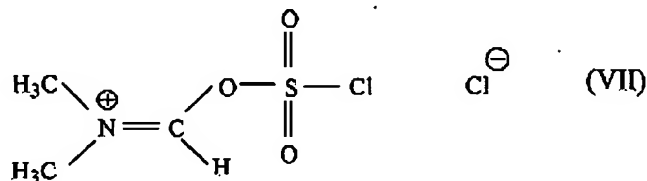
-CH<sub>2</sub>COOR<sub>5</sub>, or -C(CH<sub>3</sub>)<sub>2</sub>COOR<sub>5</sub>

wherein R<sub>5</sub> is hydrogen; or ~~an easily a~~ hydrolysable ester group selected from lower alkyl esters; alkanoyloxy alkyl esters selected from acetoxy methyl, pivaloxy methyl, 1-acetoxy ethyl, and 1-pivaloxyethyl; lower alkoxy carbonyloxyalkyl esters; alkoxymethyl esters; lower alkyl amino methyl; benzyl ester; and cyanomethyl ester[[.]]

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with N, N-dimethylformiminium chloride chlorosulphate of formula (VII)

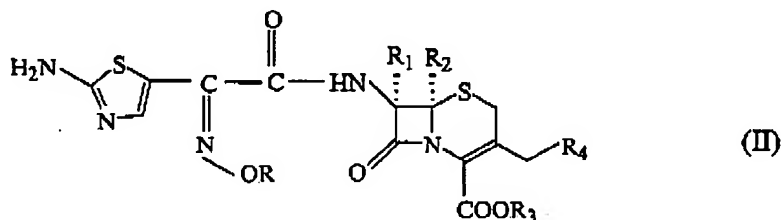


in an organic solvent at a temperature ranging from  $-30^{\circ}\text{C}$  to  $-15^{\circ}\text{C}$ .

3. (Currently Amended) ~~A~~The process according to Claim 2, wherein the organic solvent is ~~selected from chlorinated solvents such as~~ selected from dichloromethane, dichloroethane, ~~or and~~ chloroform; aromatic hydrocarbons ~~such as~~ selected from benzene ~~or and~~ toluene; and nitriles ~~such as~~ selected from acetonitrile, propionitrile ~~or and~~ butyronitrile.

4. (Currently Amended) ~~A~~The process according to Claim 2, wherein the molar ratio of compound of formula (VII) to compound of formula (IV<sup>1</sup>) is between 1.1 to 1.3.

5. (Currently Amended) A process for preparation of a cephalosporin compound of formula (II),



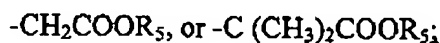
wherein

R is hydrogen, C<sub>1-4</sub> alkyl group, ~~an easily removable a hydroxyl protective group;~~ selected from trialkyl silyl ethers; trialkyl aryl silyl ethers; trialkyl stannyl ethers; trityl;

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tetrahydropyranyl; alkyl or aryl sulphonates selected from tosyl, mesyl, and besyl; boron or aluminum containing two alkyl groups; unsubstituted benzyl; or



wherein  $\text{R}_5$  is hydrogen; or ~~an easily~~ a hydrolysable ester group selected from lower alkyl esters; alkanoyloxy alkyl esters selected from acetoxy methyl, pivaloxy methyl, 1-acetoxy ethyl, and 1-pivaloxyethyl; lower alkoxy carbonyloxyalkyl esters; alkoxy methyl esters; lower alkyl amino methyl; benzyl ester; and cyanomethyl ester[[.]].

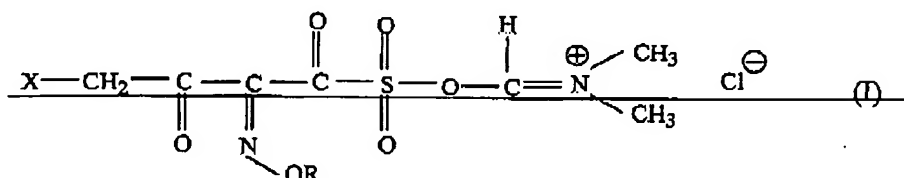
$\text{R}_1$  is hydrogen or  $[-]\text{OCH}_3$ ;

$\text{R}_2$  is hydrogen;

$\text{R}_3$  is hydrogen, a negative charge or ~~together with the  $\text{COO}^-$  group to which  $\text{R}_3$  is attached is an ester, or an alkali or alkaline earth metal, ester~~ selected from the group of lower alkyl esters; alkanoyloxy alkyl esters selected from acetoxy methyl, pivaloxymethyl, 1-acetoxyethyl, and 1-pivaloxyethyl ester; lower alkoxy carbonyloxyalkyl esters selected from methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl and 1-isopropoxycarbonyloxy-ethyl ester; alkoxy methyl esters; lower alkyl aminomethyl esters; acetamidomethyl ester; benzyl ester; and cyanomethyl ester,

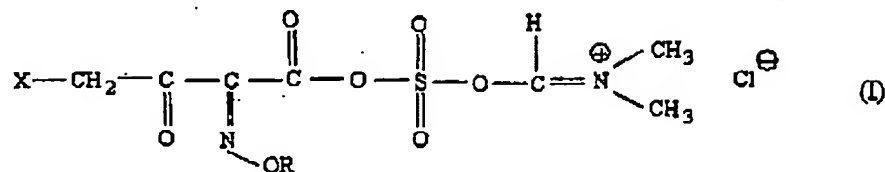
$\text{R}_4$  is hydrogen or is a substituent ~~useful in cephalosporin chemistry~~ selected from unsubstituted and substituted alkyl; and unsubstituted and substituted alkenyl; wherein substituted alkyl and/or alkenyl being substituted by alkoxy, heterocyclithio, heterocyclylcarbonylthio, alkylcarbonyloxy, or heterocyclyl;

comprising reaction of compound of formula (I)



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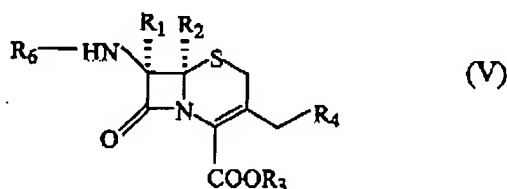


wherein X is chlorine or bromine; R and R<sub>5</sub> are selected from corresponding groups listed for those of formula (II) above

~~R is hydrogen, C<sub>1-4</sub> alkyl group, an easily removable hydroxyl protective group, -CH<sub>2</sub>COOR<sub>5</sub>, or -C(CH<sub>3</sub>)<sub>2</sub>COOR<sub>5</sub>~~

~~wherein R<sub>5</sub> is hydrogen or an easily hydrolysable ester group~~

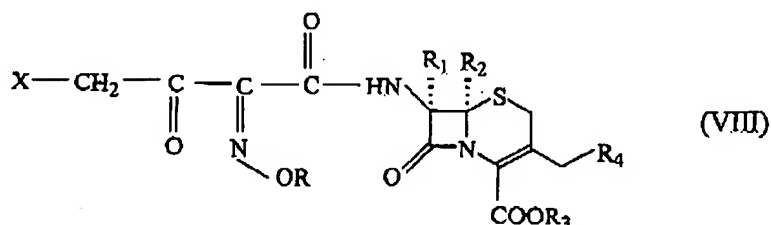
with 7-amino cephalosporanic acid of formula (V),



wherein  $R_1$  is hydrogen or  $OCH_3$ ; and  $R_2$  are selected from corresponding groups listed for those of formula (II) above;  $R_3$  is selected from a group listed for  $R_3$  of formula (II) above or a trialkyl silyl group; ~~hydrogen, a negative charge or together with the  $COO^-$  group to which  $R_2$  is attached is an ester, or an alkali or alkaline earth metal, or is a silyl group;~~  $R_4$  is selected from a group listed for  $R_4$  of formula (II) above; ~~hydrogen or is a substituent useful in cephalosporin chemistry;~~  $R_6$  is hydrogen or a trialkyl silyl group with the proviso that, when  $R_3$  is hydrogen,  $R_6$  is also hydrogen; when  $R_3$  is a trialkyl silyl group,  $R_6$  is also a trialkyl silyl group; and when  $R_3$  is an ester, ~~or an alkali or alkaline earth metal~~  $R_6$  is hydrogen

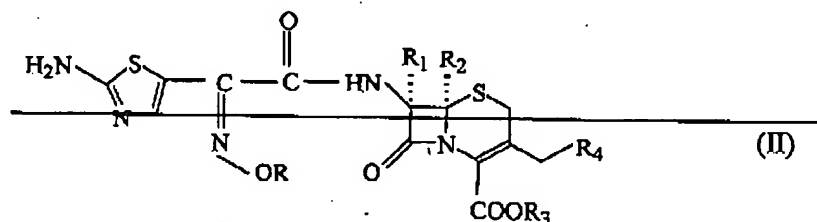
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to give 7-[(4-halo-2-oxyimino-3-oxobutyramido)-3-substituted-3-cephem-4-carboxylic acid of formula (VIII),



wherein X, R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> have are corresponding groups listed for those of formula (I) or (II) above ~~the same meanings as defined herein earlier, and R<sub>3</sub> is hydrogen, a negative charge or together with the COO<sup>-</sup> group to which R<sub>3</sub> is attached is an ester, or an alkali or alkaline earth metal.~~

followed by cyclisation of compound (VIII) with thiourea, ~~to give compound of formula (II),~~



wherein R and R<sub>3</sub> are as defined above; R<sub>1</sub> is hydrogen or ~~OCH<sub>3</sub>~~; R<sub>2</sub> is hydrogen; R<sub>3</sub> is hydrogen, a negative charge or together with the COO<sup>-</sup> group to which R<sub>3</sub> is attached is an ester or an alkali or alkaline earth metal; R<sub>4</sub> is hydrogen or is a substituent useful in cephalosporin chemistry.

6. (Currently amended) ~~A~~The process according to Claim 5, wherein the reaction of compound (I) and compound (V) to give compound (VIII) is carried out in an organic

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solvent and in the presence of a base at a temperature ranging from  $-80^{\circ}\text{C}$  to  $-15^{\circ}\text{C}$ [[.]].

7. (Currently amended) ~~A~~The process according to Claim [[5]]6, wherein the ~~the~~ organic solvent is selected from chlorinated solvents ~~such as dichloromethane, dichloroethane, and chloroform~~; aromatic hydrocarbons ~~such as benzene and toluene~~; nitrile solvents ~~such as acetonitrile, propionitrile and butyronitrile~~; and ethers ~~such as tetrahydrofuran and dioxane~~.

8. (Currently amended) ~~A~~The process according to Claim [[5]]6, wherein the base is selected from N, N dimethyl aniline, diethyl amine, and pyridine.

9. (Currently amended) ~~A~~The process according to Claim 5, wherein the molar ratio of compound (I) to the cephalosporin compound (V) is between 1.1 to 2.0; ~~preferably between 1.2 to 1.5~~.

10. (Currently Amended) ~~A~~The process according to Claim 5, wherein the preferred temperature is between  $-55^{\circ}\text{C}$  to  $-25^{\circ}\text{C}$ .

11. (Currently Amended) ~~A~~The process according to Claim 5, wherein the reaction of compound (VIII) and thiourea to give the cephalosporin compounds of formula (II) is carried out in a mixture of organic solvent and water and in the presence of a base at low to ambient temperature.

12. (Currently Amended) ~~A~~The process according to Claim [[5]]11, wherein the ~~the~~ organic solvent is selected from chlorinated solvents ~~such as dichloromethane, dichloroethane, and chloroform~~; aromatic hydrocarbons ~~such as benzene and toluene~~;

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~~nitrile solvents such as acetonitrile, propionitrile and butyronitrile; and ethers such as tetrahydrofuran and dioxane.~~

13. (Currently Amended) ~~A~~The process according to Claim [[5]]6, wherein the base is selected from alkali metal carbonates, such as sodium carbonate, potassium carbonate and lithium carbonate; alkali metal hydrogen carbonates, such as sodium hydrogen carbonate and potassium carbonate; and alkali metal acetates, such as sodium acetate and potassium acetate.

14. (Currently Amended) ~~A~~The process according to Claim 5, wherein the a  
temperature at which the reaction is carried out is between -5° C to 40° C, preferably  
~~between -10° C to 30° C.~~

15. (Currently Amended) ~~A~~The process according to Claim 5, wherein the compound  
of formula (II) is any one of

- i) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid i.e. cefdinir,
- ii) 7-[(Z)-2-(2-amino-4-thiazolyl)-2-methoxyimino)acetyl]amino-3-[(1Z)-2-(4-methyl-5-thiazolyl)ethenyl]-3-cephem-4-carboxylic acid, i.e. cefditoren and the pivaloyloxymethyl ester i. e. cefditoren pivoxil,
- iii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-methylpyrrolodino) methyl-3-cephem-4-carboxylate i.e. cefepime,



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- iv) 7-[(Z)-2-(2-aminothiazol-4-yl)methoxyiminoacetamido]-3-methyl-3-cephem-4-carboxylic acid i.e. cefetamet, and the pivaloyloxymethyl ester i. e. cefetamet pivoxil,
- v) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid i.e. cefixime,
- vi) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[1-methyl-1H-tetrazol-5-yl]thio]methyl]-3-cephem-4-carboxylic acid i.e. cefmenoxime,
- vii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[[5-carboxymethyl)-4-methyl-2-thiazolyl]thio]methyl]-3-cephem-4-carboxylic acid i.e. cefodizime,
- viii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[2,3-dihydro-2-(2-hydroxyethyl)-3-imino-1H-pyrazol-1-yl]methyl]-3-cephem-4-carboxylic acid i. e. cefoselis,
- ix) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporanic acid i.e. cefotaxime,
- x) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[92,3-cyclopenteno-1-pyridinium)methyl]-3-cephem-4-carboxylic acid i.e. cefpirome,

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- xi) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate- i.e. cefpodoxime and the 1-methylethoxycarbonyloxy ether i. e. cefpodoxime proxetil,
- xii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl-5,6,7-tetrahydroquinolinium-4-carboxylic acid inner salt i. e. cefquinome,
- xiii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methylethyl)oximinoacetamido]-3-[pyridinium]methyl-3-cephem-4-carboxylacid acid inner salt i. e. ceftazidime,
- xiv) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(5-methyl-1,2,3,4-tetrazoyl)-methyl-3-cephem-4-carboxylic acid i. e. cefteram and the and the pivaloyloxymethyl ester i. e. cefteram pivoxil,
- xv) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[2-furanylcarbonyl)thio]methyl]- 3-cephem-4-carboxylic acid i. e. ceftiofur,
- xvi) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylic acid i. e. ceftizoxime,
- xvii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid i. e. ceftriaxone, and
- xviii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1,2,3-thiadiazol-5-ylthio)methyl]- 3-cephem-4-carboxylic acid i. e. cefuzonam.

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16. (New) The compound of formula (I) according to Claim 1, wherein  $R_5$  is lower alkyl ester selected from methyl, ethyl, and tertiary butyl; lower alkoxycarbonyloxyalkyl ester selected from methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl, and 1-isopropoxycarbonyloxy ethyl; methoxymethyl ester; or acetamidomethyl ester.

17. (New) The process according to Claim 2, wherein  $R_5$  is lower alkyl ester selected from methyl, ethyl, and tertiary butyl; lower alkoxycarbonyloxyalkyl ester selected from methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl, and 1-isopropoxycarbonyloxy ethyl; methoxymethyl ester; and acetamidomethyl ester.

18. (New) The process according to Claim 5, wherein  $R_5$  is lower alkyl ester selected from methyl, ethyl, and tertiary butyl; lower alkoxycarbonyloxyalkyl ester selected from methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl, and 1-isopropoxycarbonyloxy ethyl; methoxymethyl ester; and acetamidomethyl ester.

19. (New) The process according to Claim 5, wherein  $R_3$  is lower alkyl ester selected from methyl, ethyl and tertiary butyl; and methoxymethyl ester.

20. (New) The process according to Claim 6, wherein the organic solvent is chlorinated solvent selected from dichloromethane, dichloroethane, and chloroform; aromatic hydrocarbon selected from benzene and toluene; nitrile solvent selected from acetonitrile, propionitrile, and butyronitrile; or ethers selected from tetrahydrofuran and dioxane.

21. (New) The process according to Claim 11, wherein the organic solvent is chlorinated solvent selected from dichloromethane, dichloroethane, and chloroform; aromatic hydrocarbon selected from benzene and toluene; nitrile solvent selected from acetonitrile, propionitrile, and butyronitrile; or ethers selected from tetrahydrofuran and dioxane.